REMARKS

Claims 1-60 are currently pending in this application. Claims 1, 4, 5, 7, 8, 10, 11, 13, 14, 21, 23, 27, 28, 34, 38, 39, 43, 51, and 52 are amended. Claims 17, 18, 20, 30, 31, 33, 54, 55, and 57 are withdrawn from consideration as being drawn to non-elected inventions. Claims 45-47 and 56 are allowed. Claims 9, 15, 50, and 53 were objected to as being dependent on rejected claims, but are allowable if rewritten as independent claims.

Claim amendments

Claims 1, 23, and 34 have been amended to include a limitation such that the claimed antibody comprises a heavy chain variable region. Claim 21 has been amended to include a limitation such that the claimed antibody comprises a heavy and a light chain variable region. Claims 4, 5, 7, 8, 10, 11, 13, 14, 27, 28, 38, and 39 have been amended such that they now require a higher percent identity to a disclosed sequence than they previously did. Claim 43 has been amended for purposes of clarification.

Claim Rejections - 35 USC §112, first paragraph, Enablement

Claims 1-8, 10-14, 16, 19, 21-29, 32, 34-44, 48-49, 51-52, and 58-60 stand rejected under 35 USC §112, first paragraph as not enabled. The Office Action asserts that "[i]n view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention." Office Action, page 3. The Office Action contains specific comments regarding the enablement of the claims in light of Applicants' previous response, each of which is addressed below. Office Action, page 3.

Responses to the stated reasons for a finding of non-enablement

In a previous response, Applicants had stated that claims specifying only characteristics of a heavy chain variable region (e.g. claims 1, 23, and 34) are enabled because it has been demonstrated in the art that a heavy chain variable region alone can bind an antigen. *See e.g.* US Patent No. 6,248,516. The present Office Action states:

> *"Unlike the assertion of Applicants' that the '516 patent teaches the antigen binding of heavy chain variable regions, the '516 patent actually teaches the expression construct which express both heavy and light chains as a single chain format (col. 24-25 overlapping paragraph) and the binding of antigen is contributed from both heavy and light chains (co-expression of heavy and light chains, example 11)."*

Office Action, page 3. Applicants agree that Example 5 of the '516 patent does describe the binding of both the heavy and light chain variable regions together (referred as an "Fv fragment") to lysozyme, but do not see the relevance of this fact and do not see how this fact contradicts anything in Applicants' previous response. The '516 patent also clearly describes the binding of a heavy chain variable region (and mutated derivatives thereof) alone (referred to as "VHLYS") to lysozyme. '516 patent, col. 3, lines 48-54; paragraph spanning col. 24 and 25; col. 25, lines 24-37; col. 25, lines 9-46; col. 27, lines 53-67; col. 30, lines 53-59. Thus, based on this knowledge in the art, Applicants believe that they have enabled claims, such as claims 1, 23, and 34, in which the sequence limitations of the claims are directed only to the heavy or light chain variable region. In fact, knowing that a heavy chain variable region alone can bind to antigen makes protection of this aspect of Applicants' invention particularly important.

The Office Action also comments that the previously cited Klimka reference "teaches grafting of CDR3 and other CDRs are present." Office Action, page 3. Again, Applicants agree that in Klimka, all six CDRs of the heavy and light chain variable regions were present in the scFvs that were subjected to selection and, in some cases, further testing. However, what Klimka shows is that an scFv containing a humanized heavy chain variable region, which has very limited similarity outside of CDR3 to the parental mouse antibody, binds to the same antigen (CD-30) and epitope as the parental mouse antibody and also inhibits CD-30 shedding, like the parental antibody. Klimka, entire article, especially, page 259, left col., first full paragraph and right col., second full paragraph. This finding supports Applicants assertion that a heavy chain CDR3 plays a pivotal role in determining the binding properties of an antibody. Even though other sequences may also be required, it is clear from Klimka that a variety of other sequences can produce an antibody with similar properties, provided that the heavy chain CDR3 is undisturbed. Therefore, given the knowledge in the art, a claim directed to an antibody comprising a heavy chain variable region that specifies only the sequence of a heavy chain CDR3 is fully enabled.

The Office Action further states that the "instant application does not provide any guidance that amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin." It has been known in the art for more than a decade that, in any antibody in which the question has been experimentally addressed, the CDRs are the portion of any antibody that make the closest physical contact with the antigen. *See e.g.* Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication No. 91-3242, 1991, at p. xv (enclosed, which is cited and incorporated by reference in the instant application at p. 12, lines 28-20, p. 25, lines 17-18). Hence, even though this has not been explicitly demonstrated for the antibodies described in the instant application, Applicants submit that general structural properties, which all antibodies tested have, should be also ascribed to the antibodies of the instant application. As is explained in the Specification (page 25, lines 23-32), antibodies have a well known tertiary structure and many invariant and highly conserved amino acid residues that are important for structure and/or function. Thus, the general structural and sequence constraints on antibodies are well-known in the art. Moreover, the law does not require, and applicants preferably should not, describe what is already well known in the art. *Falkner v. Inglis,* 79 U.S.P.Q.2d 1001, 448 F.3d 1357, at 1365 (Fed. Cir. 2006), citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987).

Finally, the Office Action states that the instant application "does not show any working example demonstrating a heavy chain or light chain alone which exhibits antigen binding or the antibody fragment consisting of only CDR3 region determines binding specificity." The specification does show that antibodies containing the same disclosed heavy chain variable region (SEQ ID NO:14) can bind to IFN-γ when accompanied by a light chain variable region that is either SEQ ID NO:16 (antibody 1121) or SEQ ID NO:31 (antibody 1121*). SEQ ID NO:16 and SEQ ID NO:31 have particularly disparate sequences in their CDR3s. *Compare* the sequence of 1121 to that of 1121* in Figure 13. Similarly, antibodies comprising the same disclosed light chain variable region (SEQ ID

NO:12) can bind to IFN-γ when accompanied by a heavy chain variable region that is either SEQ ID NO:10 (antibody 1118) or SEQ ID NO:30 (1118*). Specification, page 58, lines 20-23, pages 60-61, Table 3. Therefore, some of the disclosed variable regions can bind to IFN-γ in the company of more than one heavy or light chain partner. This demonstration, along with knowledge in the art that variable regions can bind as monomers, shows that claims with sequence limitations directed to only one variable region are enabled. Second, while Applicants agree that the application does not demonstrate that an antibody fragment consisting only of CDR3 will bind IFN-γ, such is not presently claimed. The amendments to independent claims 1, 21, 23, 34 submitted herewith, make it clear that all claimed antibodies comprise at least a heavy chain variable region. Thus, a molecule consisting of only CDR3 is not claimed, and enablement of such a claim is not at issue.

Factually Relevant Caselaw and Its Application to the Facts of the Instant Application

The situations in *In re Wands* and *Ex parte Mark* are analogous to the instant situation. *In re Wands*, 8 USPQ2d 1400, 858 F.2d 731 (Fed. Cir. 1988); *Ex parte Mark*, 12 USPQ2D 1904 (BPAI 1984). Below Applicants highlight the facts and claims of these cases, showing how the pending claims are clearly enabled under these cases.

In *Wands,* the broadest claim recited:

> *1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:*
>
> *contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and*
>
> *determining the presence of said substance in said sample;*
>
> *wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinant of at least* 10^9 M^1.

It was not contested that the methods of the claims could be practiced using readily available starting materials and either well-known methods or methods described in the specification. As the court put it, "The sole issue is whether, in this particular case, it would require undue experimentation to produce high affinity IgM monoclonal antibodies." Wands had used a commercially available assay kit to screen for high affinity antibodies and submitted a declaration stating that antibodies that showed more than 50,000 cpm in the assay were very likely to have affinity greater than 10^9 M^{-1}. Making monoclonal antibodies with a known antigen and the screening techniques used were found to be routine in the art, despite the fact that some considerable labor was involved. Further, nine antibodies that scored over 50,000 cpm in the assay were selected for further testing, and four of these were found to have a binding affinity constant of at least 10^9 M^{-1}. Given this high success rate, the court found the claims enabled.

Applying the well-know *Wands* factors to claims 1-8, 10-14, 16, 19, 21-29, 32, 34-44, 48-49, 51-52, and 58-60, Applicants point out that the claims (other than claims 41-44) are directed to anti-IFN-γ antibodies with particular sequence constraints. Thus, the pending claims are narrower than those of Wands, which contain no structural constraints on the antibody specified by the claims. Further, the functional constraints of claims 41-44 are comparable to that in *Wands.* All claims that are not limited to a particular sequence have a functional limitation, that is, binding to IFN-γ. Five species that fall with in the scope of the claims have been reduced to practice, that is, antibodies 1118, 1118*, 1119, 1121, and 1121*. This is one more species than the four identified in *Wands.* Numerous other variants are described in the Specification. *See e.g.* Specification, pp. 17-25, pp. 32-36, and pp. 39-40. Finally, Applicants point out that, given the technology described in, *e.g.*, Klimka et al., Ditzel et al., Barbas et al., Radar et al., and Beiboer et al. (see IDS filed January 26, 2006), among many others, it would be routine experimentation to make and select antibodies with sequences altered somewhat from the disclosed sequences in the instant application and to test them for binding to IFN-γ. Moreover, the level of skill in the art and the predictability in the art are higher than they were in *Wands,* given scientific progress in the interim. Thus, since the claims of *Wands* are enabled, the claims in the instant application are also enabled under the *Wands* standard.

In *Ex parte Mark*, a representative disputed claim read:

> *1. A synthetic mutein of a biologically active native protein in which native protein has at least one cysteine residue that is free to form a disulfide link*

> *and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.*

Based on the description of experimental steps given in the specification, which was paralleled by an inventor's declaration, the Board found that the experimentation required to determine proteins, other than those used as examples in the specification, that are suitable for use in the invention was not undue.

Looking to the facts of the instant application in view of *Mark* and the *Wands* factors, Applicants note that the rejected claims are subject to a functional constraint (binding to IFN-γ) that is much narrower than that in *Mark* ("biological activity"). Further, most of the rejected claims (other than 41-44) have, in addition, sequence-based structural constraints, as compared to the *Mark* claims, which have the constraint that the mutein starts with a "native protein." Thus, the instant claims are narrower than those in *Mark*. As described in the specification, antibodies with sequences that vary somewhat from the disclosed sequences can be made (Specification, pp. 39-49) and tested for sequence identity (Specification, pp. 19-20) and binding to IFN-γ (Specification, p. 57). Further, numerous authors in the art have described altering antibody sequences *in vitro* and efficiently selecting from groups of such variant antibodies individual antibodies having desired properties. *See e.g.*, Yang et al., Desiderio et al., Schier et al., Barbas et al., Ditzel et al., Klimka et al., and Beiboer (all of record). Therefore, the experimentation required in order to make and test variant antibodies is routine, disclosed, and not undue. As illustrated by the references cited immediately above and many others within the art, the level of skill in the art is high. Further, the application discloses five antibodies within the scope of the claims that have been reduced to practice (i.e., the 1118, 1118*, 1119, 1121, and 1121* antibodies), as compared to the three in *Mark*. *Mark*, 12 USPQ2d 1904, at 1906). Finally, the skill in the art and the predictability in the art has become higher since the time of *Mark*. Thus, because the claims in *Mark* are enabled, the narrower claims of the instant application are also enabled.

In view of the above discussion and the discussion of record as set forth in the Response to the Office Action mailed September 26, 2005, Applicants submit that the claims are enabled, and respectfully request that this ground of rejection be withdrawn. If the claims are not considered enabled, Applicants request clarification as to how this could be in light of the caselaw discussed above and guidance as to how the claims could be amended to make them allowable.

Claim Rejections - 35 USC §112, first paragraph—Written Description

Claims 1-8, 10-14, 16, 19, 21-29, 32, 34-40, 48-49, 51-52, and 58-60 stand rejected under 35 USC §112, first paragraph for failing to comply with the written description requirement.

The Office Action states;

> *"The phrase "at least 90% sequence identity to SEQ ID NO:32" as in claim 11 include 1.16 x 10^{33} different amino acid combinations. Claims as drafted are not limited to include variants with known structural and functional property as Applicants assert but encompass any isolated antibody of 50 amino acid sequences of SEQ ID NOs:6, 10 or 14."*

Applicants' representative is not aware of how the number 1.16 x 10^{33} was determined. However, the actual number is not an important issue since the number of individual, although highly similar, sequences encompassed by "at least 90% identical" would not be small. Although this number may suggest that the claim is exceedingly broad, it is still much narrower than the ultimately allowable claims at issue in *Wands* and *Mark,* which contained no structural limitations. Moreover, the sequences encompassed by "at least 90% identical" will be highly similar and, therefore, likely to have similar biological functions. All of the instant claims that are not limited to an exact sequence for a variable region also specify that the antibody specifically binds to IFN-γ. Therefore, all variants encompassed by the claims have a known functional property, and variants without this property are outside the scope of the claims. As explained above, the variants encompassed by the claims could easily be obtained by one of skill in the art, given the description in the Specification and the knowledge in the art. Therefore, even though Applicants are not presently in actual possession of every variant encompassed by the claims, one of skill in the art would know that variants with a limited amount of sequence variation from the disclosed sequences that can bind IFN-γ are within the scope of the disclosure. Further, many claims that state a degree of sequence identity also specify a minimum length, 50 amino acids, for the alignment between the compared sequences. Applicants request clarification with respect to the Examiner's apparent concern with this limitation and guidance as to whether amendment of this limitation might be helpful.

At page 4, the Office Action cites *Fiers v. Revel* for the proposition that "adequate written description requires more than a mere statement that it is part of the invention." As discussed in *Noelle v. Lederman*, the Federal Circuit has noted that the written description case law, including *Fiers* cited above, have limited precedential value and that each written description case must be decided on its own facts. *Noelle v. Lederman,* 355 F.3d 1343, 1349 (Fed. Cir. 2004). The court in *Noelle* proceeded to discuss *Enzo Biochem v. Gen-Probe*, stating that written description is satisfied where an applicant provides a functional characteristic of the invention and correlates the function with a structure. *Noelle v. Lederman* citing *Enzo Biochem v. Gen-Probe,* 323 F.3d 956, 964 (Fed. Cir. 2002). In the present case, as discussed above, Applicants have provided a function (*e.g.* binding to IFN-γ) for the claimed antibodies, as well as structure (sequence) that the claimed antibodies have in common (that is the antibodies are at least 90% identical to a particularly disclosed sequence). However, the Office Action, at page 4, also states that "conception…cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred." As pointed out in MPEP §2163.II.A.3:

> *What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed...Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species.*

Referring to the above-cited section of the MPEP, the Federal Circuit noted that an applicant is not required "to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed." *In re Wallach,* 378 F.3d 1330, 1334 (Fed. Cir. 2004). Applicants respectfully submit, as in the above-cited example from the molecular biology arts, it is unnecessary to provide explicit disclosure of every sequence or list every permutation that is 90% identical to the sequences of the invention, particularly because those of skill in the art can readily envision every sequence that falls within the 90% limitation. Applicants note that the number of such sequences is very large as discussed above, but submit that the state of the art has developed such that it is a routine matter to actually write out every sequence that is 90% identical to the disclosed sequences, whether by hand or using a computer algorithm to generate the sequences. Applicants respectfully submit, therefore, that the present disclosure of the sequences from which the claimed variants are derived and the functional property requirement of the variants of those sequences is sufficient to demonstrate to those of skill in the art that Applicants were in possession of the claimed invention at the time of filing the instant application.

Moreover, as discussed in the Response to the Office Action mailed September 26, 2005, Applicants have demonstrated actual possession of plural species within the scope of individual subparts of the rejected claims, *i.e.*, antibodies 1118, 1118*, 1119, 1121, and 1121*. For example, subpart (a) of claim 23 claims an antibody comprising a sequence at least 96% identical to SEQ ID NO: 6. The percent identity between the 1118 and 1119 heavy chain variable regions (SEQ ID NOS: 10 and 6, respectively) is about 97.436% and that between the 1119 and 1121 variable regions (SEQ ID NOS: 6 and 14, respectively) and the 1118* and 1119 variable regions (SEQ ID NOS: 30 and 6, respectively) are about 99.1% and 96.6%, respectively. Thus, the 1118, 1118*, 1121, and 1119 heavy chain variable regions all fall within the scope of subpart (a) of claim 23. Such comparisons show that each subpart of claim 23 is supported by plural species within it. Similarly, the percent identities between the 1118 and 1119 (SEQ ID NOS: 12 and 8), the 1118 and 1121* (SEQ ID NOS: 12 and 31), and the 1118 and 1121 (SEQ ID NOS: 12 and 16) light chain variable regions are, respectively, about 99%, 87%, and 99%, respectively. Therefore, the SEQ ID NOS: 8, 12, and 16 all fall within the scope of subpart (b) of claim 34. Similarly, all subparts of claim 34, with the exception of subpart (d), are supported by plural species. Therefore, the disclosure includes multiple species within the scope of individual subparts, i.e., (a), (b), etc., of, for example, claims 23, 24, 27, 34 and 35, and also species that bind to IFN-γ that are outside the percent identity specified by some of the claims. The disclosure of multiple species within the scope of the claims strengthens the written description.

In the instant application, a number of claims (e.g., 23 and 34) encompass antibodies that have a given percent identity to disclosed sequences while retaining the ability to bind IFN-γ. Other claims (such as, for example, claims 1 and 2) encompass antibodies that can bind to IFN-γ comprising one or more CDRs with at least a given number of the amino acids in a given sequence in the same order and spacing as they occur in that sequence. The specification provides an assay that will identify antibodies that bind to IFN-γ. Specification, p. 57. The disclosure of plural species within the scope of many of the rejected claims, along with the predictable nature of the art, would lead one of skill in the art to conclude that Applicants were in possession of the common attributes of the claimed antibodies.

The Office Action refers Applicants to the Revised Interim Guidelines for Examination of Patent Application Under the 35 USC § 112 ¶ 1 "Written Description" (hereinafter, the Interim Guidelines). In the Response filed January 26, 2006, Applicants cited the Synopsis of Application of Written Description Guidelines, *available at* http://www.uspto.gov/web/menu/written.pdf (hereinafter, the Synopsis). The Synopsis provides factual scenarios in the biotechnological arts to aid Examiners in applying the Interim Guidelines cited in the Office Action. Applicants previously argued based on Example 14 of the Synopsis that claims such as pending claims 23 or 34, which are closely analogous to those in Example 14 of the Synopsis, should meet the written description requirement if the guidance of the Synopsis is applied. Response filed January 26, 2006, pp. 21-22. Applicants refer the Examiner to this argument, rather than reiterating the same arguments here. The Office Action makes no comment on these arguments and offers no explanation as to why the guidance of Example 14 of the Synopsis would not apply to claims such as claims 23 and 34. Applicants request clarification as to why such guidance would not be applicable in this case and/or as to what claim amendments might bring the claims into a condition such that Example 14 would apply.

Claim Rejections - 35 USC §112, first paragraph—New Matter

Claims 41-44 are rejected under 35 USC §112 as containing new matter. Specifically, the Action states that there is no written description for the phrase "wherein the antibody cannot inhibit the biological activity of a mutated version of human IFN-γ in which the histidine at position 19 has been replaced with aspartate and/or in which the serine at position 20 has been replaced with a proline."

MPEP 2163.07 indicates that a phrase does not have to be explicitly recited to satisfy the written description requirement. In addition, by disclosing a device that inherently performs a function or has an advantage, a patent application inherently discloses that function, even if it says nothing explicit about it. MPEP 2163.07(a). Thus, Applicants note that the phrase "wherein the antibody cannot inhibit the biological activity of a mutated version of human IFN-γ in which the histidine at position 19 has been replaced with aspartate and/or in which the serine at position 20 has been replaced with a proline" is inherently described in the specification, for example, at page 66 (Table 5, and lines 3-8, all reproduced below).

> As summarized in Table 5, the 1119 antibody was able to neutralize or inhibit the biological activity of human IFN-γ and all the substitution mutants of human IFNγ except for huIFNγD19 and huIFNγP20. As in the previous example, the cynomolgus IFN-γ protein was also not inhibited by the 1119 antibody. This analysis indicates that residues 19 and 20 are particularly important for the interaction between the 1119 antibody and IFN-γ and may serve as points of contact between the 1119 antibody and human IFN-γ. (Page 66, lines 3-8)

Table 5

IFN-γ	**% Neutralization by 1119**
Human IFN-γ	100
Cynomolgus IFN-γ	0
huIFN-γD19	0
huIFN-γP20	0
huIFN-γD31	103
huIFN-γR34	109
huIFN-γR65	109
huIFN-γI77	108
huIFN-γS103	102

huIFN-γV110	103
huIFN-γI126	109

Table 5 shows that antibody 1119 cannot neutralize or inhibit the biological activity of human IFN-γ having an aspartate at position 19 or a proline at position 20. Therefore, new matter has not been introduced into the claims.

The Action also stated that deleting "fully human" and adding "antibody is human or humanized" broadens the scope of the invention and is not supported by the specification. Applicants note that support for this phrase is found, for example, at page 10, lines 20-21, which states "further, any of the antibodies of the invention can be humanized antibodies or fully human antibodies." Moreover, a slight increase in the breadth of dependent claims 42 and 44 does not seem to be relevant to a new matter issue. If this is still an issue, Applicants request clarification as to how claims 42 and 44, in their current form, present a new matter issue.

Applicants submit that the claims satisfy the requirements of 35 USC §112, and respectfully request that this ground of rejection be withdrawn.

Claim Rejections - 35 USC §102

Claims 41 and 43 are rejected under 35 USC §102(b) as anticipated by Thakur *et al.* (Molecular Immunology, 1999, vol. 36:1107-1115).

Thakur teaches an antibody (AF2) that inhibits biological activity of human IFN-γ and does not inhibit biological activity of rhesus IFN-γ, which is the same as cynomolgus IFN-γ, as previously discussed and as acknowledged in the Office Action. In determining which amino acids were necessary for AF2 activity, Thakur points out that 9 residues differ between human and rhesus IFN-γ, including 19, 20, 31, 34, 65, 77, 103, 110, and 126. In addition, the human IFN-γ amino acid sequence contains an additional amino acid at position 135 relative to the rhesus sequence. Thakur, Table 1 on page 1112. Confusingly, the Office Action states that the "positions 19, 20, and 65 are the positions where variability in amino acid sequences exhibited within the primates." Office Action page 6. Applicants request clarification as to why all other sites of variability were ignored and what the significance of this is. There are additional sites that vary in other primates. Thakur, Table 1. Thakur's experiments demonstrated that, in spite of these differences, only the human amino acids at positions 65 and 103 of IFN-γ were essential for AF2 activity. Thakur explicitly teaches that changing residues 65 and 103 of rhesus IFN-γ to the residues found in human IFN-γ completely restored AF2 neutralization activity (page 1113). In contrast, as shown in Table 6 of the instant specification (page 66 and reproduced below), the same change in cynomolgus IFN-γ (cyno IFNγ S65/L103) did not restore neutralization of an antibody of the invention.

Table 6

Construct	**Neutralization by 1119**
human IFNγ	yes
cyno IFNγ	no
cyno IFNγ H19/S20	no
cyno IFNγ S65	no
cyno IFNγ L103	no
cyno IFNγ S65/L103	no
cyno IFNγ H19/S20/S65	yes
cyno IFNγ H19/S20/L103	yes
cyno IFNγ H19/S20/L103/I110	yes
cyno IFNγ H19/S20/S65/L103/I110	yes

While the AF2 antibody requires human amino acids at positions 65 and 103 in IFN-γ for binding specificity, the claimed antibodies require human residues at positions 19 and/or 20 for neutralizing human IFN-γ activity and residues 19 and 20 for neutralizing cynomolgus IFN-γ. Thakur teaches that a chimeric interferon gamma consisting of amino acids 1-29 of the rhesus sequence and 30-143 of human sequence can be neutralized by AF2. Thakur, Table 2. Thus, the amino acids at positions 19 and 20 of human interferon gamma are not implicated in AF2's ability to neutralize interferon gamma, since Thakur explicitly teaches that species comprising the rhesus sequence at these positions is recognized by their antibody. As stated in MPEP §2131, a claim is anticipated only if each and every element as set forth in the claim is described, either expressly or inherently, in a single prior art reference. According to the data in Table 2 of Thakur et al., the AF2 antibody can inhibit a mutated version of human IFN-γ in which the histidine at position 19 has been replaced with aspartate and/or in which the serine at position 20 has been replaced with a proline (as in the rhesus sequence) and therefore does not anticipate claim 41. Similarly, since AF2 requires the human amino acid at both positions 65 and 103, it does not anticipate claim 43. Therefore, Thakur does not anticipate the instant claims.

Claim Rejections - 35 USC §103

Claims 41-44 stand rejected under 35 USC §103(a) as obvious over Thakur *et al.* (Molecular Immunology, 1999, vol. 36:1107-1115) in view of US Patent No. 6,075,181 (the '181 patent). The Action states that the '181 patent teaches fully human IFN-γ antibodies and that one of skill in the art would have been motivated to combine the teachings of Thakur with the'181 patent to generate fully human antibodies immunospecific for human IFN-γ.

As stated in MPEP § 2143, to establish a *prima facie* case of obviousness, the cited references must teach or suggest every claim limitation. As discussed above, claims 41 and 43 each contain limitations not possessed by the AF2 antibody taught by Thakur. Specifically, Thakur does not teach or suggest that amino acids at residues 19 and/or 20 of human IFN-γ are essential for AF2 neutralizing activity. Rather, Thakur taught that the IFN-γ neutralizing activity of AF2 antibody requires the presence of serine at residue 65 of IFN-γ and leucine at residue 103 of IFN-γ. Therefore, one of skill in the art would not have been motivated to make changes at IFN-γ residues 19 and/or 20, or any other amino acid residues that are different between human and rhesus monkey IFN-γ, because Thakur explicitly taught that only residues 65 and 103 of IFN-γ were important for AF2 neutralizing activity. Based on Thakur, one of skill in the art would have no reason to think that residues 19 and/or 20 were important for discriminating between human and cynomolgus IFN-γ. Thus, not all limitations of the claims are taught by the cited references, and Applicants submit that the claims are nonobvious over the combination of Thakur and the '181 patent.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned representative as indicated below at 312-913-0001.

Respectfully submitted,
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